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627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

A Phase 1 Study Evaluating PRT2527, a Potent and Highly Selective CDK9 Inhibitor, As Monotherapy and in Combination with Zanubrutinib in Patients with Select Relapsed/Refractory B-Cell Malignancies

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Background and Significance: PRT2527 is an investigational, potent, and highly selective cyclin-dependent kinase 9 inhibitor that is being developed for select relapsed or refractory (R/R) hematologic malignancies. CDK9, a key regulator of transcription elongation, has been studied as a potential target for therapy in transcriptionally addicted cancers that are dependent on oncogenic drivers with short half-lives. Although most of these drivers do not respond to direct inhibition, studies suggest that a subset of drivers, eg MYC, MYB, and MCL-1, may be targeted indirectly via CDK9 inhibition. Several nonselective CDK9 inhibitors have shown clinical activity in multiple tumor types, however, tolerability was poor (Mandal, et al. *Cancers (Basel).* 2021). PRT2527 has demonstrated high specificity and promising antitumor activity in preclinical studies, and a favorable tolerability profile in preliminary data from a Phase 1 study (NCT05159518) in adults with advanced solid tumors. These support further development of PRT2527 in hematologic malignancies as monotherapy and in combination with targeted agents. Combination of CDK9 inhibition and Bruton tyrosine kinase (BTK) inhibition may drive a durable response by enhancing apoptotic priming and shifting dependency toward CDK9 targets MCL1 and BFL1. Zanubrutinib (BGB-3111) is a highly selective, potent, irreversible BTK inhibitor that upregulates the proapoptotic signaling molecule BCL2 modifying factor, an endogenous inhibitor of BCL2, BCLXL, and BCLW (Kong, et al. *ChemMedChem*. 2018). PRT2527 as monotherapy or in combination with zanubrutinib may be an effective treatment option for select R/R hematologic malignancies.
Study Design and Methods: PRT2527-02 is a phase 1, open-label, multicenter, dose-escalation and dose-confirmation study evaluating safety, tolerability, recommended phase 2 dose (R2PD), and preliminary efficacy of PRT2527 as monotherapy and in combination with zanubrutinib in patients (pts) with select R/R hematologic malignancies. Pts eligible to receive PRT2527 monotherapy include those with aggressive B-cell lymphoma subtypes, mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) including Richter syndrome, and T-cell lymphoma subtypes. Pts eligible to receive PRT2527 in combination with zanubrutinib include those with aggressive B-cell lymphoma subtypes, MCL, and

CLL/SLL including Richter syndrome. Eligibility criteria include having relapsed or become refractory to standard-of-care therapy, measurable disease or requirement for treatment in accordance with disease-specific criteria for the hematologic malignancies under study, an ECOG PS of 0 to 1, and adequate bone marrow, renal, and liver function. Dose escalation will comprise successive cohorts receiving escalating doses of intravenous (IV) PRT2527 monotherapy once weekly (qw) in a 21-day cycle (cycle ≥2); pts at high risk for tumor lysis syndrome (TLS) and those receiving IV PRT2527 qw in combination with oral zanubrutinib 320 mg may have a 28- or 35-day ramp-up period during cycle 1. Dose escalation and de-escalation decisions will be guided by the prespecified Bayesian optimal interval design method based on dose-limiting toxicities (DLTs) observed in cycle 1. Dose confirmation will consist of indication-specific cohorts receiving the RP2D of PRT2527; pts at high risk for TLS and those receiving combination therapy may have weekly ramp-up dosing to reach RP2D. PRT2527 treatment will continue until disease progression or unacceptable toxicity, whichever comes first. The primary endpoints include safety, tolerability, DLTs, and RP2D of PRT2527 monotherapy and in combination with zanubrutinib. Adverse events will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Secondary endpoints include objective response rate, duration of response, duration of complete response, and pharmacokinetic profile of PRT2527 monotherapy and in combination with zanubrutinib. For descriptive analyses, continuous variables will be summarized by mean, standard deviation, median, minimum, and maximum. Response rates will be calculated with the 95% confidence interval. Time-to-event data will be analyzed using the Kaplan-Meier method. The study is open to enrollment and registered at ClinicalTrials.gov (NCT05665530).

Disclosures Cheson: *Astellas:* Consultancy; *ADC Therapeutics:* Consultancy; *AstraZeneca:* Consultancy; *Tessa:* Consultancy; *Adaptive Biotechnology:* Consultancy; *Calyx:* Consultancy, Honoraria; *Imaging Endpoints:* Consultancy, Honoraria; *Incyte:* Consultancy, Speakers Bureau; *BeiGene:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Speakers Bureau; *Pharmacyclics:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *Center for Cancer and Blood Disorders:* Current Employment; *Lilly:* Consultancy, Other: Travel, Accommodations, Expenses, Speakers Bureau; *Morphosys:* Consultancy, Speakers Bureau; *Regeneron:* Consultancy; *Symbio:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Shouse:** *Beigene, Inc.:* Speakers Bureau; *Kite Pharmaceuticals:* Consultancy, Speakers Bureau. **Assouline:** *Novartis Canada:* Research Funding; *BeiGene:* Consultancy; *Ipsen:* Consultancy; *Roche-Genentech:* Honoraria; *Janssen:* Honoraria; 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